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ORIGINAL ARTICLE

Time trends in osteoporosis risk factor profiles: a comparative analysis of risk factors, comorbidities, and medications over twelve years

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Abstract The aim of this article was to identify prevalent osteoporosis risk factors, medications and comorbidities associated with bone mineral density (BMD). Furthermore to evaluate changes in risk factor profiles over 12 years. 6285 women consecutively referred to an osteoporosis specialist clinic were included. Information of potential risk factors was obtained by questionnaire and clinical examination. Additional information on medication use, comorbidities and fractures were obtained from national registries. An association (<0.05) between well-known risk factors negatively influencing bone health was established in a real-life setting. The prevalence of osteoporosis and proportion of patient's having comorbidity's associated with osteoporosis were increasing during the inclusion period (start 23.8 %, end 29.7 %). Increasing age (OR = 1.05), current smoking (OR = 1.18), estrogen deficiency (OR = 1.7), hyperthyroidism (OR = 1.5), previous major osteoporotic fracture (OR = 1.7), former osteoporosis treatment (OR = 3.5), higher BMI (OR = 0.87), use of calcium supplementation (OR = 1.2), high exercise level (OR = 0.7), and use of thiazide diuretics (OR = 0.7) were identified as predictors of osteoporosis by DXA. Rheumatoid arthritis (OR = 2.4) and chronic pulmonary disease (OR = 1.5) was associated with site-specific osteoporosis by DXA at the total hip.

Current use of loop diuretics (OR = 1.7) and glucocorticoid use (OR = 1.04–1.06) were associated with both total hip and femoral neck T-score <-2.5. Our data confirms an independent negative association with BMD of many established risk factors, certain comorbidities, and medications. Exercise level, use of loop diuretics, and prevalent chronic pulmonary disease, risk factors not included in fracture risk calculators were associated with osteoporosis by DXA. Time trends indicate risk profile is dynamic, with increasing focus on secondary osteoporosis.

Keywords Risk factors · Women's health · Osteoporosis · Bone density · Secondary osteoporosis · Time trend

Background and introduction

Measurement of bone mineral density (BMD) is still the most widely used method of establishing a diagnosis and evaluating treatment efficacy [1]. Site-specific fracture risk is more than doubled with a decline of one standard deviation in BMD at the hip or lumbar spine [2], but increasing awareness of BMD-independent risk factors for fracture has led to a more widespread use of fracture risk algorithms [3] such as FRAX (https://www.shef.ac.uk/FRAX/).

It is well established that osteoporosis is underdiagnosed and undertreated [1]. To change this, it is essential to develop rational and cost effective strategies for identification of individuals with increased risk of fragility fracture. Increasing awareness of osteoporosis risk factors and secondary causes will help educate health care personnel and the general population. Identification of high-risk patients will presumably lead to allocation of appropriate treatment to those who might benefit the most from preventive measures and treatment.

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A dedicated and focused approach via a specialist based unit is likely to accomplish such a goal [4, 5].

Most guidelines include lists of risk factors in peri- and postmenopausal women that should lead to clinical evaluation and BMD measurements.

In Denmark, the main clinical risk factors are considered to be: age above 80, family history of osteoporosis or fractures, former fragility fracture, menopause before the age of 45, excessive alcohol intake, smoking, tendency to fall, aromatase inhibitor, or systemic glucocorticoid treatment ($\geq$5 mg daily in 3 months or 450 mg yearly). Finally some diseases are recognized that should lead to DXA evaluation.

These guidelines do, however, change over time as does the clinicians perceptions of the relative importance of different risk factors.

At our hospital, a specialist unit for osteoporosis evaluation has existed since 1979. In 1999, a database was established, including a risk factor questionnaire, biochemical data, and densitometry results from all patients referred for evaluation. Combining these data with information from national Danish registers gives information on the importance of different risk factors as well as the changing perception among referring physicians and patients of which risk factors that should lead to osteoporosis evaluation.

Materials and methods

Study population

All patients referred from general practice (GP) for osteoporosis evaluation to the Copenhagen University Hospital Hvidovre from 2000 to 2012 were eligible. A total of 8294 women underwent BMD evaluation and were before first visit requested to fill out a questionnaire regarding potential risk factors for osteoporosis. The questionnaire was returned by 6402 women (response rate of 77 %). Non-responders, patients lacking a DXA evaluation, and patients who had participated in clinical research involving prevention or treatment of osteoporosis were not included. Evaluation of hyponatremia as a possible risk factor of low bone mass and fractures in a subpopulation of this cohort of patients has previously been published [6] and supplementary description of included patients and collection of data can be found here.

In total, 6285 women were included in the univariate analysis. Due to missing values, 4599 out of 6285 women were included in the final multivariate analysis corresponding to 73.2 % of women having returned the questionnaire (Fig. 1).
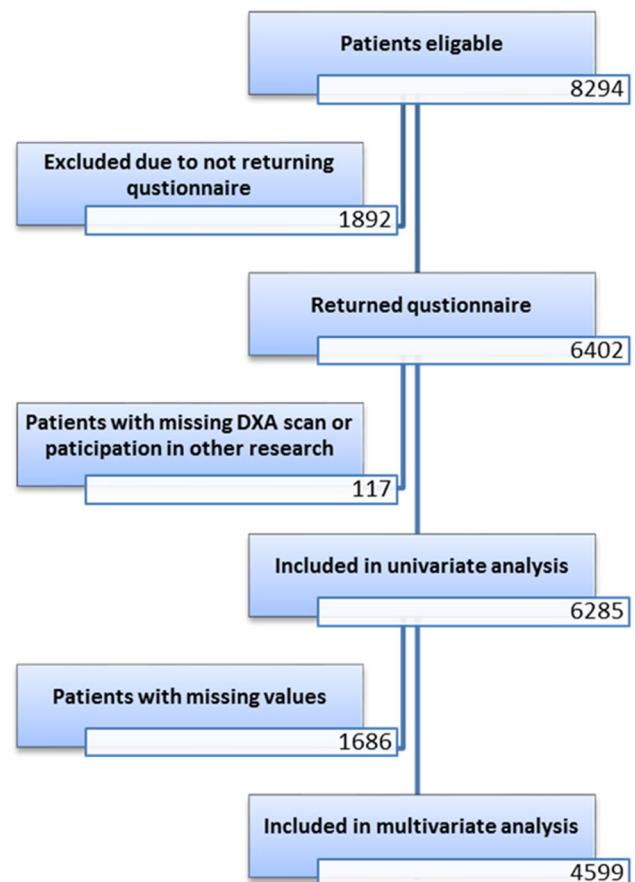

Fig. 1 Flowchart of patients included in the study. This figure shows inclusion and exclusion criteria of patients

Risk factor registration

The questionnaire was intended to address generally accepted risk factors for osteoporosis in 1999, but a few risk factors, like alcohol consumption, was not accepted by the Danish Data Protection Agency to be part of the registered information in the database. At the beginning of the study, a small number of patients were asked to fill out the questionnaire twice with at least 1 month's interval, only minor differences were detected between the two. Further, at the examination of the patients, inconsistencies and misunderstandings were corrected. The questionnaire based information included a family history of fractures in first-degree relatives, own fracture history, nutritional factors (daily consumption of milk, cheese etc.), use of calcium and vitamin D supplements, height at age 25, limitations in everyday life, physical function level, work and exercise, age of menarche and menopause, history of gynecological surgery, former estrogen replacement therapy, history of osteoporosis treatment, and current smoking status. Limitations in everyday life were classified as having no/minor or having limitations. Women with a

menopausal age <45 years of age or who had undergone ovarian surgery with the removal of both ovaries, both without use of hormone replacement therapy were considered to be estrogen deficient. Patients were categorized as being physically active if they indicated to have exercised at least once a week. Work function was classified based on sitting, standing, or weight lifting components, exemplified by different occupations.

The daily dietary calcium intake was assessed based on the self-reported average daily use of dairy products plus an estimated basal intake of calcium set at 300 mg corresponding to an approximate calcium contribution from non-dairy products in an average Danish diet. Patients were asked about daily consumption of cheese (never, 1–3 slices, more than 3 slices) and amounts of milk/yoghurt etc. being consumed (>half a liter, <half a liter, never).

Contributions from milk/yoghurt etc. were averaged as 120 mg/100 mL whereas the average calcium content of a slice of cheese was approximated at 120 mg as well based on food composition tables from the Danish National Food Agency (2010) [7]. According to their approximated minimum daily consumption, patients were divided into groups (<420, 540–780, and >900 mg/day).

Anthropometric measures included measurements of bodyweight and height. Patients were measured wearing indoor clothes and being barefooted. If the body mass index (BMI) were below 20 kg/m^2, patients were categorized as underweight. The questionnaire was used unchanged throughout the entire observation period.

Densitometry measurements

BMD measurement at the lumbar spine, femoral neck, and total hip was conducted using three types of Hologic DXA scanners (Hologic Inc., MA, USA). If bilateral artificial hips were present only BMD measurements at the lumbar spine were performed. Coefficient of variation was calculated from daily DXA scans on a standard phantom and was on the individual scanners below 0.9 % at the lumbar spine. Variation between machines was assessed. Biannually, repeated DXA scans on the same phantom comparing measurements of BMD between machines were conducted. A slight difference corresponding to approximately 1 % of the mean BMD was present between one machine and the others. The difference was deemed clinically insignificant for this study.

Spinal *T*-scores were derived from the HOLOGIC study [8]. *T*-scores of hip and femoral neck were calculated using values from the NHANES phase III study [9]. Based on the lowest measured *T*-scores (if <−2.5) at the femoral neck, total hip or lumbar spine patients were classified as having osteoporosis or not [10].

Laboratory tests

Blood samples were collected in the majority of cases and if feasible this took place on the same day as the DXA scan was performed. Blood samples were analyzed at the local biochemical department (accredited according to ISO 15189 standards) and included measurements of s-PTH, s-25(OH) vitamin D, s-TSH, and s-creatinine from which estimated glomerular filtration rate (eGFR) was calculated, as well as hemoglobin, leucocyte counts, thrombocytes, s-C-reactive protein, serum electrolytes, s-albumin, s-alkaline phosphatases, and s-ALAT. Before 2008, only patients ≥65 years had a s-25(OH)-vitamin D measurement. Onward all patients had D-vitamin status included in the standard blood samples. Patients were divided into groups based on vitamin D levels severe <12.5 nmol/L, moderate/mild <25–50 nmol/L, and normal >50 nmol/L [11]. An adjusted s-25(OH)-vitamin D was calculated as (mean s-25(OH)-vitamin D/mean s-25(OH)-vitamin D in the month of measurement) × the measured value of s-25(OH)-vitamin D.

Registers

In Denmark, every person has a unique registration code that allows detailed registration at the individual level. Registration occurs automatically and this information was consequently available for all patients in the study. This allows linkage of information collected in the clinical database with information from national administrative registers. Linkage and anonymization was done at Statistics Denmark in order to fulfill the Danish Data Protection Act [12].

In this study, information from The Danish Medicines Agency and The National Hospital Discharge Register were used.

The Danish Medicines Agency holds registers of all drugs sold at pharmacies and hereby a complete record of drugs sold from 1996 and onward exits. High-quality individual prescription data covering redeemed medications using ATC codes, dosage, and date of sale was obtained from The Danish National Prescription Registry [13]. Validity and capture of information in this register is high [13]. Patient files were manually checked for information regarding osteoporosis medicines administered at the hospital, mainly IV-bisphosphonates, and (since 2010) denosumab.

Dosages of redeemed glucocorticoids during the previous year before BMD measurement were converted to prednisolone/prednisone equivalent dosages in milligrams/day [14]. Other medications including selective serotonin receptor inhibitors (SSRI), tricyclic anti-

depressants (TCA), and thiazides were evaluated and defined daily dosages (DDD) during the previous year were calculated. Current use of loop diuretics was thought present if a patient had redeemed any prescriptions within the previous year. In each tablet of angiotensin II inhibitors/ Thiazide combinations, the content of thiazide was set to ½ DDD, unless other dosage was certain.

The Danish National Patient Register [15] provided data on comorbidities and prevalent fractures. The register is regarded as the most comprehensive of its kind and holds information covering the period from 1977 to present (1977–1994 inpatients only, thereafter outpatient and emergency visits as well). Individual contacts are registered and coded using the ICD-8/ICD-10 system. This register has nationwide coverage and captures almost all contacts [15]. It has been reported to be accurate especially for the registration of fractures, where a precision of 97 % has been reported [14, 16].

Fractures were registered according to fracture site and identified as major osteoporotic fractures (MOF = femoral, vertebral, humeral, lower arm) or others.

Prevalent individual comorbidities were defined as a registration of the disease in question in the register up to 3 months after first visit. This was done in order to allow chronic diseases identified during osteoporosis evaluation to be included. A history of hyperthyroidism or diabetes type II where also deemed positive if patients had filled any prescription of oral antidiabetics or oral antithyroid medication predating the date of the first visit. A Charlson Comorbidity Index score was calculated and used to adjust for differences in overall comorbidity [17]. Patients were categorized as having a disease associated with osteoporosis (including treatment with aromatase inhibitors and glucocorticoids >450 mg/previous year) based on national treatment guidelines. (See supplementary material for detailed information regarding collected data, ICD-8/ICD-10, ATC codes etc.)

Endpoints

Evaluated outcomes were risk factor associations with T-scores and overall/site-specific osteoporosis by DXA in the total hip, femoral neck, or lumbar spine at the time of referral.

Change in risk profile and prevalence of diseases associated with osteoporosis in patients seen in the period of 2000–2004, 2005–2008, and 2009–2012 was assessed.

Statistics

SAS software (version 9.3) was used for the statistical analysis. Descriptive variables are presented as mean value with standard deviation (±SD) or medians with interquartile range (IQR) for continues variables. Categorical variables are presented as number and percent of responders.

Difference in characteristics of patients who filled the questionnaire and patients failing to do so with regard to BMD and age were analyzed using the Student's t test for continuous variables. Further comparisons were done using χ^2, or Wilcoxon two sample tests.

Correlation analysis between variables was performed using Spearman's analysis. Uni- and multivariate regression analysis were performed using generalized linear models. Whenever unequal group variances were detected, p values was calculated using Welch test. Predictors of prevalent osteoporosis were identified by logistic regression.

Sub analyses in osteoporosis treatment naive patients were performed.

Age was tested as an interaction term. Age stratification sub-analysis (Table 5) was performed when a positive effect modification on explanatory variables was identified. When risk factors were thought to represent more or less the same only one where included in the multivariate analysis. A wide array of different comorbidities and medicinal products was not assed or included in multivariate analysis due to low prevalence.

Statistical significance was defined as a two-tailed p value <0.05.

Results

Included patients had a mean age of 61.2 (± 11.7) years. In total 1857 (29.6 %) women had a T-score of less than −2.5 at either measuring site. A T-score below −2.5 in the lumbar spine was evident in 1489 (23.7 %) of patients, whereas 611 (9.8 %) and 848 (13.8 %) had a T-score in the osteoporotic range at the total hip and femoral neck region. Patient characteristics are presented in Table 1. Patients not included in the study were slightly older (mean difference −2.34 years, CI −3.04; −1.65) and had a marginally lower T-score in the total hip (mean difference 0.19, CI 0.13–0.25) and femoral neck (mean difference 0.17, CI 0.11–0.22) as compared to patients included in the study.

When comparing patients seen in 2000–2004, 2005–2008, and 2009–2012, we found that a significantly higher (overall $p = 0.0004$) proportion of patients included in the later periods had prevalent osteoporosis and a medical condition associated with osteoporosis. As such, 23.8, 26.5, and 29.7 % of patients had a registration of one of the mentioned medical conditions at the time of BMD measurement. Furthermore, (Table 2) a dramatic drop in the proportion of current smokers ($p = >0.001$) as well as an increase in the proportion of patients having received

Table 1 Patient characteristics

General characteristics		Medicine use	
Age, mean (±SD)	61.2 (11.7)	Loop diuretics DDD per day, median (IQR)	0.82 (0.36; 1.64)
BMI, mean (±SD)	24.1 (4.4)	Users of loop diuretics, no (%)	358 (5.7 %)
Underweight, no (%)	863 (15.0)	Thiazide DDD per day, median (IQR)	0.68 (0.48–1.37)
T-score total hip, mean (±SD)	−1.12 (1.10)	Users of Thiazide, no (%)	1080 (17.2 %)
T-score spine, mean (±SD)	−1.47 (1.44)	Prednisone EQ mg/during 1 year, median (IQR)	4.11 (1.03–7.19)
T-score femoral neck, mean (±SD)	−1.45 (0.99)	Users of prednisone within 1 year, no (%)	526 (8.4 %)
Blood samples		Prednisolone EQ > 450 mg/year, no (%)	386 (6.1 %)
S-PTH mmol/L, median (IQR)	3.2 (2.2–4.4)	SSRI per day, median (IQR)	0.82 (0.32;1.10)
S-vitamin D level nmol/L, no (%)		Users of SSRI within 1 year, no (%)	508 (8.1 %)
Normal (>50)	2375 (76.5 %)	TCA per day, median (IQR)	0.47 (0.11–0.69)
Low (12.5–50)	704 (22.7 %)	Users of TCA within 1 year, no (%)	141 (2.2 %)
Very low (<12.5)	27 (0.87 %)	Former osteoporosis treatment, no (%)	1112 (17.7 %)
GFR < 30 mL/min/1.73 m^2, no (%)	39 (0.64 %)		
Questionnaire		*Comorbidities*	
Fractures in first-degree relatives, no (%)		Charlson comorbidity index, median (IQR)	0 (0–1)
Yes	2952 (47.5 %)	Hyperthyroidism, no (%)	226 (3.6 %)
No	2928 (47.1 %)	Alcohol-related diagnosis, no (%)	224 (3.6 %)
Do not know	339 (5.5 %)	Diabetes type II, no (%)	229 (3.6 %)
Dietary calcium, no (%)		Rheumatoid arthritis, no (%)	150 (2.4 %)
High	1397 (22.6 %)	Chronic pulmonary disease, no (%)	618 (9.8 %)
Medium	2820 (45.5 %)	Inflammatory bowel disease, no (%)	91 (1.5 %)
Low	1979 (31.9 %)	Former MOF fracture, no (%)	1303 (20.7 %)
Smoking, no (%)	1758 (28.6 %)	Former fracture all, no (%)	2113 (33.6 %)
Exercise YN, no (%)	4130 (69.3 %)	Former fracture upper arm, no (%)	363 (5.8 %)
Estrogen deficiency, no (%)	494 (9.1 %)	Former fracture lower arm, no (%)	797 (12.7 %)
Limitations in daily life, no (%)	894 (15.3 %)	Former fracture hip, no (%)	177 (2.8 %)
Manual labor, no (%)	1932 (33.1 %)	Former fracture femur non-hip, no (%)	28 (0.5 %)
Vitamin D supplementation; no (%)	3090 (54.5 %)	Former fracture spine, no (%)	164 (2.6 %)
Calcium supplementation, no (%)	3757 (63.3 %)	Former fracture other, no (%)	1204 (19.2 %)

This table shows mean values with standard deviations (SD), or medians with interquartile range (IQR) for continues variables. Medicine doses presented are among current users. Categorical variables are presented as number and percent of observations of those who responded

S-PTH serum parathyroid hormone, *eGFR* estimated glomerular filtration rate, *DDD* defined daily dosages, *EQ* equivalents, *TCA* tricyclic anti-depressives, *SSRI* selective serotonin reuptake inhibitors, *MOF* major osteoporotic fractures

Numbers and percentages are of those with available data

anti-osteoporotic treatment was evident. Among others an increasing proportion of patients having CPD, diabetes, MOF, and using calcium supplements were evident. Age and BMI of patients was slightly higher in the later inclusion period.

Results of the univariate analysis are presented in Table 3.

Subsequent multiple regression (Table 4) revealed age, BMI, glucocorticoid use within 1 year, a history of CPD, low-daily dietary consumption of calcium, current smoking, low exercise level, former osteoporosis treatment, former MOF, estrogen deficiency, rheumatoid arthritis

(RA), prevalent alcohol-related diagnoses, and use of loop diuretics, to be independent risk factors associated with lower *T*-scores in the total hip. Treatment with thiazides was associated with a higher *T*-score.

The mentioned risk factors accounted for approximately 35 % of the variance in total hip BMD.

Of the mentioned significant associations in the total hip only glucocorticoids use, alcohol consumption and RA were not found to have the same association with low *T*-score at the femoral neck. Furthermore a family history of fractures was associated with low femoral neck *T*-scores. R^2 in the femoral neck was 0.31.

Table 2 Time trend: prevalence of risk factors at time of BMD measurement

	2000–2004	2005–2008	2009–2013	Overall p value
Osteoporosis[#] (%)	27.0	30.7	30.8	0.010*
Age (mean)	60.1	62.0	61.2	(first vs. last) 0.010*
BMI (mean)	23.8	24.1	24.4	(first vs. last) <0.0001*
Chronic pulmonary disease (%)	8.4	10.5	10.6	0.033*
Smoking (%)	33.3	28.0	23.5	>0.0001*
Exercise (%)	69.2	68.8	70.1	0.70
Dietary calcium high (%)	22.1	23.3	21.8	
Dietary calcium medium (%)	45.6	45.2	46.0	0.82
Dietary calcium low (%)	32.3	31.5	32.2	
Estrogen deficient (%)	8.4	9.7	8.7	0.28
Hyperthyroidism (%)	3.5	3.6	3.8	0.86
Rheumatoid arthritis (%)	2.2	2.5	2.4	0.77
Family history of fractures (%)	50.3	46.5	45.5	0.010*
Inflammatory bowel disease (%)	1.2	1.5	1.9	0.23
Type II diabetes (%)	3.0	3.6	4.7	0.033*
Major osteoporotic fracture (%)	18.3	21.9	21.8	0.0038*
Osteoporosis treatment (%)	14.1	17.4	22.8	>0.0001*
Alcohol-related diagnosis (%)	2.9	4.0	3.7	0.16
Calcium supplement (%)	59.4	63.1	69.0	>0.0001*
SSRI use (%)	7.7	8.2	8.4	0.77
Thiazide use (%)	15.4	18.4	17.6	0.024*
Loop diuretics use (%)	5.2	5.9	6.0	0.50
>450 mg prednisone EQ use previous year (%)	7.2	5.3	6.2	0.027*
TCA use (%)	2.2	2.5	1.9	0.47

This table shows the prevalence in percent and statistical test (χ^2) of overall difference between periods

EQ equivalent, *TCA* tricyclic anti-depressives, *SSRI* selective serotonin reuptake inhibitors, *BMI* body mass index

Numbers and percentages are of those with available data

[#] $T < -2.5$ in total hip, femoral neck or lumbar spine; * $p < 0.05$

Fewer significant associations were identified at the lumbar spine. As such high age, estrogen deficiency, former MOF, former osteoporosis treatment, hyperthyroidism, low BMI, low exercise level, and family history of fractures were found to be associated with lower spinal bone mass. Loop diuretic and thiazide use were associated with a higher T-score.

At all sites an association of taking calcium supplements with low BMI was found to be present.

Effect modification/interaction with age is shown in Table 5.

At the lumbar spine, multiple interactions with age were detected.

Age stratification among others showed use of loop diuretics to be statistically associated with higher spinal T-scores in only the +75-year olds. Higher Charlson score was associated with lower lumbar spinal T-score in patients between 50 and 75 years of age. Thiazide use on the other hand was associated with higher T-scores in the lumbar spine in people above the age of 50.

When evaluating the association of potential risk factors with osteoporosis by DXA (T-score <-2.5 at any site), fewer risk factors were identified (Table 6). Age, estrogen deficiency, hyperthyroidism, prevalent MOF, former osteoporosis treatment, lower BMI, taking calcium supplementation, current smoking, no exercise, and using less thiazides were significantly associated with a higher OR of having osteoporosis. Furthermore RA and CPD was associated with osteoporosis by DXA at the total hip. Current use of loop diuretics and glucocorticoid use was associated with both total hip and femoral neck T-score below -2.5.

Discussion

In this study, we were able to demonstrate a clear independent association between many of the reviewed risk factors and low BMD in a population of predominantly postmenopausal women. Possible risk factors often not included in different risk calculators, i.e., exercise level,

Table 3 Univariate analysis

Parameter	Total hip (95 % CI)	Pr > |t|	Neck (95 % CI)	Pr > |t|	Spine (95 % CI)	Pr > |t|
Age	−0.034 (−0.036 to −0.032)	<0.0001	−0.033 (−0.035 to −0.031)	<0.0001	−0.019 (−0.022 to 0.016)	<0.0001
BMI	0.085 (0.079–0.091)	<0.0001	0.064 (0.058–0.069)	<0.0001	0.077 (0.069–0.085)	<0.0001
Underweight (BMI <20)	−0.71 (−0.78 to −0.63)	<0.0001	−0.51 (−0.59 to −0.44)	<0.0001	−0.59 (−0.69 to −0.48)	<0.0001
eGFR < 30 mL/min/1.73 m²	−0.66 (−1.01 to −0.30)	0.0003	−0.60 (−0.92 to −0.28)	0.0003	0.44 (−0.021 to 0.91)	0.061
Severe vitamin D deficiency vs. normal	−0.37 (−0.80 to 0.061)	0.092	−0.35 (−0.73 to 0.036)	0.075	−0.53 (−1.11 to 0.043)	0.070
Mild/moderate vitamin D deficiency vs. normal	0.055 (−0.039 to 0.15)	0.25	0.084 (0.0001–0.17)	0.050	0.093 (−0.034 to 0.22)	0.15
Severe month corrected vitamin D deficiency vs. normal	−0.42 (−0.86 to 0.031)	0.068	−0.42 (−0.82 to −0.019)	0.040	−0.53 (−1.13 to 0.064)	0.080
Mild/moderate month corrected vitamin D deficiency vs. normal	0.024 (−0.073 to 0.12)	0.63	0.061 (−0.025 to 0.15)	0.16	0.097 (−0.034 to 0.23)	0.15
Family fractures	0.11 (0.054–0.17)	0.0001	0.052 (0.00048–0.10)	0.048	−0.015 (−0.089 to 0.058)	0.68
Dietary calcium low vs. medium	0.018 (−0.046 to 0.081)	0.58	−0.0010 (−0.068 to 0.047)	0.72	0.0068 (−0.076 to 0.090)	0.87
Dietary calcium low vs. high	−0.041 (−0.12 to 0.034)	0.29	−0.023 (−0.091 to 0.046)	0.51	−0.046 (−0.14 to 0.053)	0.36
Current smoking	−0.24 (−0.30 to −0.18)	<0.0001	−0.12 (−0.18 to −0.068)	<0.0001	−0.16 (−0.24 to −0.076)	0.0001
Exercise more than once a week.	0.17 (0.11–0.23)	<0.0001	0.13 (0.075–0.18)	<0.0001	0.038 (−0.041 to 0.11)	0.36
Estrogen deficiency	−0.24 (−0.34 to −0.14)	<0.0001	−0.17 (−0.26 to −0.081)	0.0002	−0.34 (−0.47 to −0.21)	<0.0001
Limitations in daily activities	−0.59 (−0.67 to −0.51)	<0.0001	−0.49 (−0.56 to −0.42)	<0.0001	−0.22 (−0.32 to −0.12)	0.0002
Manual labor	−0.22 (−0.28 to −0.16)	<0.0001	−0.18 (−0.23 to −0.12)	<0.0001	−0.11 (−0.19 to −0.036)	0.0053
D-vitamin supplement	−0.26 (−0.32 to −0.20)	<0.0001	−0.25 (−0.30 to −0.19)	<0.0001	−0.31 (−0.39 to −0.24)	<0.0001
Calcium supplement	−0.37 (−0.43 to −0.31)	<0.0001	−0.35 (−0.40 to −0.30)	<0.0001	−0.44 (−0.52 to −0.37)	<0.0001
Current loop diuretics use	−0.47 (−0.59 to −0.35)	<0.0001	−0.45 (−0.56 to −0.34)	<0.0001	0.12 (−0.036 to 0.27)	0.19
Thiazide use (DDD/day)	0.074 (0.013–0.13)	0.018	0.017 (−0.038 to 0.072)	0.55	0.27 (0.19–0.35)	<0.0001
Glucocorticoid use (prednisone EQ doses/day)	−0.021 (−0.033 to −0.0097)	0.0003	−0.016 (−0.026 to −0.0055)	0.0028	−0.0012 (−0.016 to 0.014)	0.87
>450 mg prednisolone equivalent dosages the previous year	−0.24 (−0.36 to −0.13)	0.0003	−0.20 (−0.30 to −0.095)	0.0002	0.084 (−0.064 to 0.23)	0.32
SSRI use (DDD/day)	0.013 (−0.079 to 0.10)	0.79	0.023 (−0.060 to 0.11)	0.58	0.16 (0.038–0.28)	0.0097
TCA use (DDD/day)	−0.11 (−0.46 to 0.24)	0.53	−0.059 (−0.38 to 0.26)	0.72	−0.26 (−0.72 to 0.19)	0.26
Osteoporosis treatment	−0.87 (−0.94 to −0.80)	<0.0001	−0.79 (−0.85 to −0.73)	<0.0001	−1.01 (−1.10 to −0.92)	<0.0001
Charlson index	−0.12 (−0.14 to −0.096)	<0.0001	−0.099 (−0.12 to −0.080)	<0.0001	−0.052 (−0.080 to −0.024)	0.0003
Hyperthyroidism	−0.26 (−0.41 to −0.11)	0.0021	−0.26 (−0.39 to −0.13)	0.0001	−0.24 (−0.43 to −0.050)	0.014
Alcohol-related diagnosis	−0.28 (−0.43 to −0.13)	0.0002	−0.14 (−0.27 to −0.−0.0071)	0.039	0.053 (−0.14 to 0.24)	0.59
Type II diabetes	0.17 (0.022–0.31)	0.024	0.093 (−0.039 to 0.23)	0.17	0.38 (0.19–0.57)	<0.0001
Rheumatoid arthritis	−0.27 (−0.45 to −0.092)	0.014	−0.16 (−0.33 to −0.0001)	0.049	−0.10 (−0.34 to 0.13)	0.46
Chronic pulmonary disease	−0.36 (−0.45 to −0.27)	<0.0001	−0.33 (−0.41 to −0.24)	<0.0001	−0.18 (−0.30 to −0.057)	0.0038
Inflammatory bowel disease	−0.19 (−0.42 to 0.034)	0.096	−0.16 (−0.36 to 0.050)	0.14	−0.15 (−0.44 to 0.15)	0.33
Prevalent fractures MOF	−0.56 (−0.63 to −0.49)	<0.0001	−0.50 (−0.56 to −0.44)	<0.0001	−0.45 (−0.54 to −0.37)	<0.0001

Table 3 continued

Parameter	Total hip (95 % CI)	$Pr > |t|$	Neck (95 % CI)	$Pr > |t|$	Spine (95 % CI)	$Pr > |t|$
All	−0.43 (−0.49 to −0.37)	<0.0001	−0.40 (−0.45 to −0.35)	<0.0001	−0.35 (−0.28 to −0.43)	<0.0001
Upper arm	−0.48 (−0.60 to −0.37)	<0.0001	−0.44 (−0.55 to −0.34)	<0.0001	−0.36 (−0.51 to −0.21)	<0.0001
Lower arm	−0.44 (−0.52 to −0.36)	<0.0001	−0.42 (−0.49 to −0.34)	<0.0001	−0.40 (−0.51 to −0.30)	<0.0001
Hip	−1.25 (−1.42 to −1.08)	<0.0001	−1.01 (−1.16 to −0.85)	<0.0001	−0.57 (−0.79 to −0.36)	<0.0001
Femur non-hip	−0.54 (−0.99 to −0.10)	0.016	−0.13 (−0.52 to 0.27)	0.53	−0.44 (−0.97 to 0.099)	0.11
Spine	−0.54 (−0.71 to −0.36)	<0.0001	−0.44 (−0.60 to −0.29)	<0.0001	−0.36 (−0.58 to −0.14)	0.0017
Other fractures	−0.18 (−0.25 to −0.11)	<0.0001	−0.19 (−0.25 to −0.13)	<0.0001	−0.14 (−0.23 to −0.048)	0.0027

Association with T-score at the total hip, femoral neck and lumbar spine

This table shows the estimated changes in T-score for one unit change in the explanatory variable

For prevalent comorbidities and other binary covariates in the univariate analysis, the estimated changes in T-score are for the presence of the risk factor listed in table. For other risk factors, estimates show effect of: Age (increase of 1 year), BMI (1 kg/m² increase), Thiazide use (increase in one DDD/day), SSRI use (increase in one DDD/day), TCA use (increase in one DDD/day), Charlson index (increase of one score) Glucocorticoid use (increase in one prednisone EQ doses/day)

Approximations of dietary calcium: low dietary calcium = <420 mg/day, medium dietary calcium = 540–720 mg/day, high dietary calcium = >900 mg/day

Severe vitamin D deficiency = <12.5 nmol/L, mild/moderate vitamin D deficiency = 12.5–50 nmol/L, normal = D-vitamin > 50 nmol/L

eGFR estimated glomerular filtration rate, *DDD* defined daily dosages, *EQ* equivalent, *TCA* tricyclic anti-depressives, *SSRI* selective serotonin reuptake inhibitors, *MOF* major osteoporotic fractures

Table 4 Multivariate analysis

Parameter	Total HIP (95 % CI)	Pr > |t|	HIPNECK (95 %CI)	Pr > |t|	Spine (95 % CI)	Pr > |t|
Age	−0.030 (−0.033 to −0.027)	<0.0001	−0.029 (−0.031 to −0.027)	<0.0001	−0.016 (−0.020 to −0.012)	<0.0001
Charlson Index	−0.020 (−0.043 to 0.0035)	0.096	−0.0088 (−0.030 to 0.013)	0.42	−0.011 (−0.044 to 0.023)	0.54
Estrogen deficient	−0.21 (−0.30 to −0.12)	<0.0001	−0.18 (−0.27 to −0.10)	<0.0001	−0.31 (−0.44 to −0.18)	<.0001
Hyperthyroidism	−0.033 (−0.18 to 0.11)	0.66	−0.083 (−0.22 to 0.052)	0.23	−0.24 (−0.45 to −0.024)	0.029
Rheumatoid Arthritis	−0.23 (−0.41 to −0.056)	0.0098	−0.096 (−0.26 to 0.067)	0.25	−0.14 (−0.39 to 0.12)	0.30
Prevalent MOF	−0.31 (−0.38 to −0.24)	<0.0001	−0.26 (−0.32 to −0.20)	<0.0001	−0.29 (−0.38 to −0.19)	<0.0001
Osteoporosis treatment	−0.49 (−0.57 to −0.42)	<0.0001	−0.45 (−0.51 to −0.38)	<0.0001	−0.77 (−0.88 to −0.66)	<0.0001
BMI	0.094 (0.088–0.10)	<0.0001	0.071 (0.066–0.077)	<0.0001	0.076 (0.067–0.084)	<0.0001
Glucocorticoid use	−0.019 (−0.032 to −0.0059)	0.0043	−0.011 (−0.023 to 0.00070)	0.065	−0.0077 (−0.027 to 0.011)	0.43
Chronic pulmonary disease	−0.12 (−0.21 to −0.027)	0.012	−0.12 (−0.20 to −0.031)	0.0080	−0.055 (−0.19 to 0.082)	0.43
High dietary calcium	0.073 (0.0027–0.14)	0.042	0.084 (0.018–0.15)	0.013	0.069 (−0.035 to 0.17)	0.20
Medium dietary calcium	0.074 (0.014–0.13)	0.015	0.042 (−0.014 to 0.098)	0.14	0.043 (−0.045 to 0.13)	0.34
Calcium Supplement	−0.12 (−0.17 to −0.062)	<0.0001	−0.11 (−0.17 to −0.063)	<0.0001	−0.22 (−0.30 to −0.14)	<0.0001
Family fractures	−0.021 (−0.074 to 0.032)	0.44	−0.065 (−0.11 to −0.015)	0.010	−0.10 (−0.18 to −0.026)	0.0092
Current smoking	−0.18 (−0.23 to −0.12)	<0.0001	−0.096 (−0.15 to −0.041)	0.0006	−0.071 (−0.16 to 0.016)	0.11
Exercise	0.17 (0.12–0.23)	<0.0001	0.15 (0.098–0.21)	<0.0001	0.10 (0.017–0.19)	0.019
Inflammatory bowel disease	−0.074 (−0.29 to 0.15)	0.51	−0.040 (−0.24 to 0.16)	0.70	0.012 (−0.31 to 0.33)	0.94
Alcohol-related diagnosis	−0.18 (−0.32 to −0.029)	0.019	−0.055 (−0.19 to 0.081)	0.43	0.16 (−0.057 to 0.37)	0.15
Current loop diuretics use	−0.19 (−0.31 to −0.067)	0.0024	−0.19 (−0.30 to −0.076)	0.0011	0.25 (0.074–0.43)	0.0054
Thiazide diuretics use	0.083 (0.024–0.14)	0.0057	0.074 (0.019–0.13)	0.0082	0.23 (0.15–0.32)	<0.0001
Type II diabetes	0.053 (−0.099 to 0.20)	0.50	0.061 (−0.080 to 0.20)	0.40	0.15 (−0.075 to 0.37)	0.20
SSRI use	0.0089 (−0.083 to 0.10)	0.85	0.0019 (−0.084 to 0.088)	0.97	0.079 (−0.055 to 0.21)	0.25
TCA use	−0.010 (−0.35 to 0.32)	0.95	0.080 (−0.25 to 0.41)	0.63	−0.34 (−0.84 to 0.15)	0.17

Association with T-score at the total hip, femoral neck and lumbar spine

This table shows the independent effect on T-score of one unit change of the explanatory variable

For prevalent comorbidities and other binary covariates, the estimated changes in T-score are for the presence of the risk factor listed in table. Multivariate analysis includes age (increase of 1 year), current smoking, BMI (one kg/m² increase), former major osteoporotic fractures (MOF), dietary calcium intake (high vs. low and medium vs. low), rheumatoid arthritis, alcohol-related diagnosis, use of thiazide diuretics (increase in one DDD/day), current use of loop diuretics, use of selective serotonin reuptake inhibitors (increase in one SSRI DDD/day), use of tricyclic anti-depressives (increase in one TCA DDD/day), Inflammatory bowel disease, Charlson comorbidity index score (increase of one score), chronic pulmonary disease, hyperthyroidism, history of fractures in first-degree relatives, type II diabetes, former osteoporosis treatment, supplements of calcium, physical exercise level, estrogen deficiency, and use of prednisone (increase in one equivalent (EQ) doses per day during 1 year)

DDD defined daily dosages. Approximations of dietary calcium: low dietary calcium = <420 mg/day, medium dietary calcium = 540–720 mg/day, high dietary calcium = >900 mg/day

Table 5 Interactions with age

Parameter	Overall test	Stratified in age groups		
		<45 years	45–65 years	+65 years
Total hip				
Age × estrogen deficient	$p = 0.0102$	0.094 ($p = 0.58$)	−0.22 ($p = 0.0003$)	−0.31 ($p = 0.002$)
Femoral neck				
Age × glucocorticoid use	$p = 0.0419$	0.014 ($p = 0.57$)	−0.025 ($p = 0.0042$)	0.0046 ($p = 0.63$)
Age × BMI	$p = 0.0021$	0.094 ($p = {<}0.0001$)	0.068 ($p = {<}0.0001$)	0.070 ($p = {<}0.0001$)
		<50 years	50–75 years	+75 years
Lumbar spine				
Age × Charlson index	$p = 0.0267$	0.038 ($p = 0.3882$)	−0.048 ($p = 0.019$)	0.083 ($p = 0.074$)
Age × osteoporosis treatment	$p = {<}0.0001$	−0.76 ($p = 0.0029$)	−0.93 ($p = {<}0.0001$)	−0.15 ($p = 0.3018$)
Age × calcium supplement	$p = 0.0216$	−0.22 ($p = 0.016$)	−0.23 ($p = {<}0.0001$)	−0.081 ($p = 0.6172$)
Age × current loop diuretics use	$p = 0.0209$	−0.025 ($p = 0.9351$)	0.17 ($p = 0.1468$)	0.40 ($p = 0.0433$)
Age × Thiazide diuretics use	$p = 0.0148$	−0.027 ($p = 0.8924$)	0.25 ($p = {<}0.0001$)	0.28 ($p = 0.0123$)

Left-hand side: shows p values of overall test of interaction with age

Right-hand side: stratified in age groups. It shows estimated independent effect on T-score of one unit change of the explanatory variable within age groups. Age stratification in identical age groups were not possible as a positive interaction would still be present in one of the groups

CPD, and use of loop diuretics were found to be associated with low BMD and potentially add information to the estimate of risk calculators. Thiazide use on the other hand seems to have a beneficial effect on BMD, and this effect might be considered when using treatment with diuretics in patients with known or suspected osteoporosis. Our data suggest that non-smoking, higher bodyweight, not having a alcohol-related diagnosis, high exercise level as well as a high intake of dietary calcium are important with regard to preservation of bone mass and may add information on both the selection of patients for osteoporosis evaluation as well as information on modifiable lifestyle factors to be used in the general prevention of osteoporosis. Efforts should be made to optimize these aspects whenever one evaluates bone health and emphasizes the need for widespread information targeted at the general population. We found that our model accounted for 35 % of the variance of BMD at the hip thus indicating that many important factors influencing bone mass are still not accounted for. The variance explained in our model are similar to or better than other studies [18–21].

Our data indicates that the risk profile of patients being referred for osteoporosis evaluation changes over time and that the proportion of patients having a medical diagnosis associated with secondary osteoporosis (as described in the supplemental material) at the time of evaluation seems to be increasing. Our findings might reflect a general tendency toward an increased focus on diseases known to be associated with fractures and secondary osteoporosis, like

COPD and type-2 diabetes [22]. Adding all reported causes of secondary osteoporosis (diseases, use of glucocorticoids >450 mg and use of aromatase inhibitors within the previous year), an increase of 24 % in number of referred patients with suspected secondary osteoporosis was seen. This increased focus on secondary osteoporosis is important, since these patients often present with severe bone loss and/or elevated fracture risk. Correspondingly, we found osteoporosis prevalence to increase from 27.0 % in the start to 30.8 % in the later period.

A dramatic reduction in the proportion of current smokers was also observed. This could well be due to changes in Danish legislation which came into effect in May 2007 prohibiting smoking at public institutions, workplaces, bars, and restaurants.

The study has several strengths that make this study unique compared to others. Systematic prospective collection of self-reported and measured data from consecutively referred patients makes evaluation of risk factors of low bone mass in a real-life setting possible. Combining these with the Danish registry system, adds information not obtainable from the cohort itself. To our knowledge no other studies, describing overall risk factors of low BMD, have included information from the above-mentioned data sources.

The large number of women included over more than a decade as well as the ability to demonstrate a large number of independent associations when taking predictors attributable to both hereditary, life style, and comorbidity-

Table 6 Odds ratios of association with osteoporosis by DXA

Odds ratio estimates	Osteoporosis#		Osteoporosis# (untreated)		Total hip		Femoral neck		Spine	
	Estimate (95 % CI)	$Pr > \chi^2$	Estimate (95 % CI)	$Pr > \chi^2$	Estimate (95 % CI)	$Pr > \chi^2$	Estimate (95 % CI)	$Pr > \chi^2$	Estimate (95 % CI)	$Pr > \chi^2$
Age	1.049 (1.041–1.057)	<0.0001	1.055 (1.046–1.064)	<0.0001	1.081 (1.068–1.095)	<0.0001	1.083 (1.072–1.095)	<0.0001	1.031 (1.024–1.039)	<0.0001
Charlson index	1.045 (0.984–1.111)	0.15	1.072 (1.000–1.147)	0.050	1.061 (0.973–1.156)	0.18	1.063 (0.986–1.147)	0.11	1.059 (0.996–1.127)	0.069
Estrogen deficient	1.664 (1.304–2.124)	<0.0001	1.911 (1.448–2.523)	<0.0001	1.397 (0.966–2.019)	0.076	1.188 (0.855–1.651)	0.31	1.469 (1.147–1.880)	0.0023
Hyperthyroidism	1.542 (1.051–2.263)	0.027	1.205 (0.761–1.909)	0.43	1.366 (0.779–2.396)	0.28	1.155 (0.699–1.908)	0.57	1.590 (1.083–2.334)	0.018
Rheumatoid Arthritis	1.156 (0.722–1.851)	0.55	1.257 (0.708–2.234)	0.43	2.373 (1.306–0.766)	0.0046	1.082 (0.591–1.982)	0.80	1.000 (0.614–1.627)	1.00
Prevalent MOF	1.699 (1.427–2.021)	<0.0001	1.935 (1.584–2.364)	<0.0001	2.099 (1.626–2.710)	<0.0001	1.751 (1.401–2.188)	<0.0001	1.439 (1.202–1.721)	<0.0001
Osteoporosis treatment	3.520 (2.928–4.232)	<0.0001	–	–	2.383 (1.829–3.104)	<0.0001	2.473 (1.968–3.109)	<0.0001	3.184 (2.650–3.825)	<0.0001
BMI	0.868 (0.850–0.886)	<0.0001	0.872 (0.852–0.893)	<0.0001	0.765 (0.736–0.795)	<0.0001	0.816 (0.791–0.841)	<0.0001	0.889 (0.871–0.908)	<0.0001
Glucocorticoid use	1.009 (0.975–1.045)	0.59	0.998 (0.954–1.045)	0.95	1.063 (1.017–1.110)	0.0062	1.042 (1.001–1.085)	0.047	1.018 (0.983–1.054)	0.32
Chronic pulmonary disease	1.240 (0.964–1.596)	0.094	1.281 (0.961–1.706)	0.091	1.510 (1.062–2.146)	0.022	1.352 (0.989–1.847)	0.058	1.129 (0.871–1.463)	0.36
High dietary calcium	0.859 (0.704–1.049)	0.11	0.857 (0.680–1.081)	0.14	0.901 (0.658–1.233)	0.85	0.786 (0.598–1.033)	0.17	0.860 (0.700–1.056)	0.14
Medium dietary calcium	0.980 (0.828–1.159)	0.45	0.998 (0.826–1.206)	0.38	0.857 (0.651–1.127)	0.40	0.864 (0.685–1.089)	0.80	0.970 (0.816–1.153)	0.55
Calcium Supplement	1.208 (1.029–1.419)	0.021	1.275 (1.075–1.513)	0.0054	0.963 (0.734–1.263)	0.79	1.038 (0.824–1.306)	0.75	1.249 (1.055–1.478)	0.0099
Family fractures	1.130 (0.973–1.312)	0.88	1.117 (0.941–1.326)	0.24	1.057 (0.827–1.351)	0.80	1.173 (0.952–1.447)	0.53	1.147 (0.983–1.338)	0.45
Current smoking	1.180 (1.003–1.389)	0.046	1.266 (1.054–1.521)	0.012	1.450 (1.120–1.876)	0.0047	1.402 (1.124–1.749)	0.0028	1.120 (0.947–1.324)	0.19
Exercise	0.777 (0.662–0.911)	0.0019	0.738 (0.616–0.885)	0.0010	0.496 (0.388–0.634)	<0.0001	0.624 (0.505–0.772)	<0.0001	0.848 (0.719–1.001)	0.051
Inflammatory bowel disease	1.157 (0.624–12,146)	0.64	1.466 (0.710–3.027)	0.30	0.986 (0.395–2.462)	0.98	0.749 (0.323–1.736)	0.50	1.153. (0.625–2.129)	0.65
Alcohol-related diagnosis	0.982 (0.662–1.457)	0.93	0.865 (0.553–1.352)	0.53	1.378 (0.804–2.363)	0.24	1.263 (0.780–2.045)	0.34	0.838 (0.550–1.276)	0.41
Current loop diuretics use	0.922 (0.660–1.287)	0.63	0.828 (0.560–1.224)	0.34	1.728 (1.117–2.675)	0.014	1.660 (1.124–2.452)	0.011	0.659 (0.459–0.947)	0.024

Table 6 continued

Odds ratio estimates	Osteoporosis#		Osteoporosis# (untreated)		Total hip		Femoral neck		Spine	
	Estimate (95 % CI)	$Pr > \chi^2$	Estimate (95 % CI)	$Pr > \chi^2$	Estimate (95 % CI)	$Pr > \chi^2$	Estimate (95 % CI)	$Pr > \chi^2$	Estimate (95 % CI)	$Pr > \chi^2$
Thiazide diuretics use	0.723 (0.603–0.867)	0.0005	0.713 (0.577–0.880)	0.0017	0.889 (0.672–1.176)	0.41	0.865 (0.684–1.093)	0.22	0.710 (0.583–0.863)	0.0006
SSRI use	0.923 (0.706–1.207)	0.56	1.005 (0.752–1.342)	0.97	0.748 (0.470–1.189)	0.22	1.133 (0.804–1.595)	0.48	0.839 (0.625–1.127)	0.24
Type II diabetes	0.732 (0.463–1.155)	0.18	0.776 (0.467–1.292)	0.33	0.797 (0.385–1.653)	0.54	0.647 (0.345–1.213)	0.17	0.785 (0.486–1.266)	0.32
TCA use	1.246 (0.516–3.008)	0.62	1.459 (0.581–3.667)	0.42	2.376 (0.819–6.899)	0.11	1.459 (0.425–5.003)	0.55	1.308 (0.530–3.224)	0.56

Estimated odds ratios and test of associations with overall and site-specific osteoporosis

For prevalent comorbidities and other binary covariates the estimated changes in odds ratio of osteoporosis is for the presence of the risk factor listed in table

Multivariate analysis includes age (increase of 1 year), current smoking, BMI (one kg/m² increase), former major osteoporotic fractures (MOF), dietary calcium intake (high vs. low and medium vs. low), rheumatoid arthritis, alcohol-related diagnosis, use of thiazide diuretics (increase in one DDD/day), current use of loop diuretics, use of selective serotonin reuptake inhibitors (increase in one SSRI DDD/day), use of tricyclic anti-depressives (increase in one TCA DDD/day), Inflammatory bowel disease, Charlson comorbidity index score (increase of one score), Chronic pulmonary disease, hyperthyroidism, history of fractures in first-degree relatives, type II diabetes, former osteoporosis treatment, supplements of calcium, physical exercise level, estrogen deficiency, and use of prednisone (increase in one equivalent (EQ) doses per day during 1 year)

DDD defined daily dosages. Approximations of dietary calcium: Low dietary calcium = <420 mg/day, medium dietary calcium = 540–720 mg/day, high dietary calcium = >900 mg/day

$T < -2.5$ in total hip, femoral neck or lumbar spine

related causes into account also makes this study interesting. A comprehensive picture of the overall risk profile of low BMD and osteoporosis in women can thus be presented. In traditional register-based research, information on many important aspects (i.e., smoking status, family fracture history, nutritional factors, exercise status, and menopausal status) regarding other known risk factors are missing whereby conclusions might be misleading. In this study, we were able to address many of these risk factors.

This cohort represents a spectrum of patients thought to be at risk of having osteoporosis in a real-life setting. This quality can be lacking in randomized controlled trials where strict inclusion- and exclusion criteria's might limit the usefulness of the generated results in everyday life. Dowd et al. [23] evaluated participation eligibility of 120 patients with osteoporosis in 4 different ongoing RCT's and found that only 3–21 % could participate. Exclusion reasons included age, co-medication, and comorbidity.

Findings from previous studies [18, 19, 24–27] and recognized risk factors [28] for osteoporosis and fractures included in different fracture risk calculators such as FRAX are in agreement with our findings, especially when looking at the total hip or femoral neck. Furthermore risk factors recognized to have a negative effect on bone health, such as low exercise level, CPD and use of loop diuretics, were confirmed [29–31].

We found increasing doses of redeemed thiazide to be associated with higher BMD in the femur and in the lumbar spine in the +50-year old. The fact that we did not find an association in the younger age group could be due to the duration of treatment and that the younger might not have been treated for a prolonged period. Furthermore the reason why thiazide is used might also be different between age groups.

A negative association with a familial fracture history at both the femoral neck and lumbar spine was found but could not be affirmed when looking at osteoporosis status. It is possible that this association would be stronger if only a hip fracture history was considered. Fractures in first-degree relatives have been shown to be associated with a small increased risk of any fracture, osteoporotic, or hip fracture even after BMD adjustment [32] emphasizing the need to address this aspect when evaluating patients.

Regarding glucocorticoid use only the negative association with total hip T-scores and site-specific osteoporosis at the total hip and femoral neck remained statistically significant.

Analyzing glucocorticoid use based on use of more than 450 mg during the last year did not change our findings. In the full multivariate analysis, both RA and CPD were significant risk factors in predicting either overall or site-specific osteoporosis by DXA, whereas IBD was not. This is in accordance with previous studies showing chronic obstructive pulmonary disease to be independently associated with osteoporosis regardless of prednisolone use [31] and that bone loss can be present even in glucocorticoid treatment naive women with RA [33]. Predictors of overall osteoporosis did not differ significantly according to osteoporosis treatment status (Table 6) although hyperthyroidism was not found to be a predictor of overall osteoporosis in treatment naïve women.

Perhaps surprisingly the use of calcium and vitamin D supplements was found to be associated with having a lower BMD. The reason for this could be that patients recognized as being at risk of osteoporosis are more likely to start taking these supplements, as soon as this is brought to their attention. This confounding by indication may mask an actual positive effect of calcium on BMD, as has been demonstrated in several studies [34]. This is emphasized by the fact that high dietary calcium intake in our study is associated with higher T-scores in the total hip and femoral neck. We did unfortunately not have any information about the dose or duration of the calcium supplementation being used, since it is available without prescription. It is possible that examining the association with total daily intake of calcium (dietary + supplementation) would have led to another result. In Denmark, Vitamin D (calcium supplements) is an over the counter drug and a large proportion of the population is using vitamin D supplements. This might be especially common among women focused on the risk of osteoporosis as its use is recommended by the national board of health in all patients believed to be at risk of osteoporosis. For these reasons, we do not find the prevalence of vitamin D supplement use is surprising.

The associations of risk factors seem to vary with age and BMD measurement site. When relating risk factors to spinal T-score, the associations was weaker. In especially older persons, the accuracy of spinal DXA measurements is weakened by changes in the region of interest, such as vertebral deformity, scoliosis, osteophytes and extraskeletal calcification, all tending to lead to a falsely elevated BMD value [1].

This could likewise be the reason for the surprising finding of loop diuretics being associated with higher spinal T-scores in the +75-year olds in contrary to the femoral findings.

Only few interactions with age were detected in the total hip and femoral neck. This is more or less in line with recent findings [35]. In contrast, the many identified effect modifications with age make use of risk factors to identify patients with low BMD in the lumbar spine more difficult from a clinical point of view, since the patients age has to be taken into account.

This study has limitations regarding lack of information about certain possible relevant risk factors of low BMD

such as self-reported alcohol use. The prevalence of many risk factors of secondary osteoporosis was too low to be assessed. Register-based information from The National Hospital Discharge Register covers only registrations at hospital level. Underestimation of the prevalence of especially less severe cases of comorbidity such as alcoholism not treated at the hospital was thus evident. We have previously demonstrated that hyponatremia could be considered a novel risk factor of low bone mass, but did not include this as a risk factor in this paper [6]. Relating to dietary calcium intake categorization was done using approximations of minimum intake from dairy products and adding it to an approximate average contribution from non-dairy products. The use of a complex food frequency questionnaire was found to be too difficult to handle in routine clinical setting. Nevertheless conclusions made relating to dietary calcium intake must be interpreted with care as the calculated minimum intake from dietary calcium is a rough approximation. We therefore only conclude that higher intake seems to be beneficial but from these data a recommendation as to how high is not possible.

A significant amount of women did not have their D-vitamin measured before 2008. A very low percentage had very severe deficiency. In the univariate analysis, associations with *T*-scores were insignificant. After correcting for the month of which blood samples were taken, we saw a significant reduced femoral neck *T*-score in patients with severe deficiency. We defined adequate levels of vitamin D to be above 50 nmol/L for adequate skeletal health but recognize that for patients considered at risk of osteoporosis, a higher level (75 nmol/L) might be better [36].

A clear underestimation of the prevalence of spinal fractures is present, since routine x-rays of the spine was not a part of the individual evaluation and that vertebral fractures in general often remain undiagnosed, despite the presence of clinical signs [37]. We did not have any information about the trauma mechanism of fractures (high or low trauma). In order to include fractures more frequently associated with osteoporosis, only fractures at a major osteoporotic site were included. As referral is based on specific recognized risk factors some degree of selection bias cannot be excluded and this could influence generalizability of our results. It is likewise possible that patients being healthier in general are the ones being referred.

A significant limitation of this study is that we evaluated risk of low BMD and osteoporosis and not risk of experiencing a fracture. Some of the evaluated risk factors have in other studies been shown to be associated with fractures at least partly independent of BMD. The fact that we do not find these risk factors to be a predictor of low bone mass does not imply that these risk factors are unimportant in terms of fracture risk. In conclusion, a systematic collection of clinical information, questionnaire data, and individual coupling with information from the unique Danish national registries enables a platform for further studies to be established. Modifiable risk factors identified in this study could be potential candidates in a prevention strategy among the background population. Our study advocate that avoiding excessive alcohol intake and smoking, doing exercise more than once a week as well as having a relevant dietary calcium intake is likely to be beneficial. The findings of a negative association of loop diuretic use and a positive effect of thiazide diuretics with relation to *T*-scores should be considered when diuretic treatment is needed in patients with osteoporosis. Our findings furthermore emphasize the need to be aware of the negative effect of diseases such as CPD and RA, regardless of glucocorticoid use. Finally our data indicate that the risk profile of patients is changing over time and that the proportion of referred patients having a medical disorder potentially associated with increased risk of osteoporosis seems to be growing.

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